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Prognosis in advanced lung cancer – A prospective study examining key clinicopathological factors

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ABSTRACT

Objectives: In patients with advanced incurable lung cancer deciding as to the most appropriate treatment (e.g. chemotherapy or supportive care only) is challenging. In such patients the TNM classification system has reached its ceiling therefore other factors are used to assess prognosis and as such, guide treatment. Performance status (PS), weight loss and inflammatory biomarkers (Glasgow Prognostic Score (mGPS)) predict survival in advanced lung cancer however these have not been compared. This study compares key prognostic factors in advanced lung cancer.

Materials and methods: Patients with newly diagnosed advanced lung cancer were recruited and demographics, weight loss, other prognostic factors (mGPS, PS) were collected. Kaplan–Meier and Cox regression methods were used to compare these prognostic factors.

Results: 390 patients with advanced incurable lung cancer were recruited; 341 were male, median age was 66 years (IQR 59–73) and patients had stage IV non-small cell ($n = 288$) (73.8%) or extensive stage small cell lung cancer ($n = 102$) (26.2%). The median survival was 7.8 months. On multivariate analysis only performance status (HR 1.74 CI 1.50–2.02) and mGPS (HR 1.67, CI 1.40–2.00) predicted survival ($p < 0.001$). Survival at 3 months ranged from 99% (ECOG 0–1) to 74% (ECOG 2) and using mGPS, from 99% (mGPS0) to 71% (mGPS2). In combination, survival ranged from 99% (mGPS 0, ECOG 0–1) to 33% (mGPS2, ECOG 3).

Conclusion: Performance status and the mGPS are superior prognostic factors in advanced lung cancer. In combination, these improved survival prediction compared with either alone.

1. Introduction

In most patients that present with advanced lung cancer (stage III–IV), there are the options of oncology treatment (including chemotherapy, radiotherapy, targeted therapy) or best supportive care (palliative care) alone [1]. The benefits of any treatment must be balanced with the side-effects, which in cancer treatment often are considerable.

A fundamental factor influencing treatment decisions in advanced lung cancer is the expected prognosis, however clinicians are often inaccurate in survival predictions, and can have a tendency to overestimate the prognosis [2]. There are currently no good predictors of the benefit of chemotherapy; however prognosis is currently being used to select those who receive chemotherapy. The most established factor for assessing prognosis is performance status and this is advised in guidelines for lung cancer treatment [3]. Furthermore, studies have shown that many patients receive inappropriate anti-cancer treatment near the end of life [4]. Better prognostic tools are needed to avoid unnecessary, potentially harmful therapy during end of life.

In addition to performance status, various other factors have been shown to independently predict survival in advanced lung

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cancer, such as weight loss and systemic inflammation. Weight loss is common in patients presenting with lung cancer and typically worsens as disease progresses, with around 60% of patients reporting significant weight loss in their last few months of life [5]. Studies have also linked weight loss in lung cancer to reduced survival, independent of treatment received. Furthermore, patients with weight loss are less likely to complete their intended course of chemotherapy and are more likely to experience chemotoxicity than patients without weight loss, independent of tumor status [5]. Weight loss in patients with lung cancer is therefore of symptomatic, predictive and prognostic relevance.

Measures of the systemic inflammatory response are of independent prognostic value in cancer. A combination of the inflammatory markers CRP (C-reactive protein) and albumin (Alb) termed the modified Glasgow Prognostic Score (mGPS), has been the most extensively studied and validated prognostic scoring tool. The mGPS score has also been shown to correlate with weight loss in patients with advanced cancer, and is associated with increased treatment toxicity, reduced treatment response and poor nutritional status [6–8].

Although weight loss, performance status and the mGPS have been shown to be of independent prognostic value in lung cancer, they have not been compared with each other. Therefore the primary aim of the present study was to compare these prognostic factors in patients with advanced lung cancer, to assess which has the greatest prognostic value in order to guide treatment. A secondary aim was to assess if independent prognostic factors could be combined to improve survival prediction.

2. Materials and methods

A prospective observational study was conducted. Consecutive patients were recruited from two University Hospitals in Greece: the first cohort was evaluated in the University Hospital of Herakleion between 6 February 2006 and 12 October 2010 (with follow-up until 27 October 2011) and the second in University Hospital of Larissa between 30 March 2010 and 13 December 2013 (with follow-up until 1 June 2013).

Eligible patients were 18 years of age or older, had advanced lung cancer (stage IV NSCLC or extensive stage SCLC) and were due to start systemic anti-cancer therapy.

The following data were collected: sex, age, cancer type, body mass index (BMI), percentage weight loss in the preceding 3 months, performance status, albumin, CRP, and survival status at follow-up.

Age, percentage weight loss in the preceding 3 months, performance status, CRP and albumin were categorized using standard thresholds to aid comparison and stratification of results.

Performance status was measured according to the Eastern Cooperative Oncology Group (ECOG) classification which ranges from grade 0 (fully active) to grade 5 (dead). ECOG grades 0 and 1 were grouped into one category as this has been standard practice in the majority of prospective phase III trials in lung cancer and survival changes dramatically in patients with PS2 versus PS0-1 [9,10]. Age was divided into patients less than 65 years of age, between 65 and 74 years and greater than 74 years of age. Cachexia was defined as >5% weight loss, in line with the international consensus classification [11].

CRP and albumin values were used to calculate the mGPS score for each patient. The limit of detection for CRP was 5 mg/L and all samples were processed according to standardized laboratory procedures. The mGPS was calculated as follows: CRP $\leq$ 10 mg/L = 0, CRP > 10 mg/L = 1, CRP > 10 mg/L and albumin < 35 g/L = 2.

Individuals' demographic indices and categories were analyzed and compared to their survival status. Survival time was calculated in months and defined as the time from study entry until death, or censored if alive at follow-up date. Survival curves were plotted using Kaplan–Meier methods and the log-rank test was applied. Survival analysis was performed using Cox proportional hazards model and hazard ratios (HRs) were calculated. Multivariate survival analysis was conducted using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. Stratification by primary cancer site was performed for the survival analysis. Factors that were predictive of survival in the multivariate analyses were finally grouped together to assess whether they had better prognostic accuracy when grouped together.

Statistical analysis was performed using SPSS version 19. All statistical testing was conducted at the 5% level, and 95% confidence intervals (CI) are reported throughout. Where $n \leq 10$, these groups were not reported.

The study has been conducted and adheres to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines [12].

3. Results

There were 390 patients included and their demographics are detailed in Table 1. All patients had advanced incurable lung cancer (stage IV NSCLC or extensive stage SCLC). The majority of patients was male (n = 341, 87.4%) and the median age was 66 years (IQR 59–73). The median performance status was 1 (IQR 1–2). Median survival was 7.8 months (IQR 3.5–13.6) reflecting the advanced disease staging of the population. The minimum and median follow-up for survivors was 0.6 months and 12.8 months, respectively. At the time of cessation of data collection, 107 patients were alive and 283 had died. Patients had either non-small cell lung cancer (n = 288) (73.8%) or small cell lung cancer (n = 102) (26.2%).

The median weight loss in the previous three months was 5.0% (IQR 0.8–10.2). The median BMI was 25.2 (IQR 22.5–28.5).

Clinico-pathological factors and survival were compared for this cohort of patients and are detailed in Table 2. On univariate survival analysis, age (p = 0.004), sex (p = 0.009), tumor type (p = 0.007), weight loss (%) in the previous 3 months (p = 0.001), performance status (p < 0.001) and mGPS (p < 0.001) were significant predictors of survival. On multivariate analysis only performance status (p < 0.001) and mGPS (p < 0.001) were predictors of survival.

Table 1
Patient demographics (n = 390).

Parameter	n	%	Median (IQR)
Sex (M/F)	341/49	87.4/12.6	
Tumor type	288	73.8	
Non-small cell lung	102	26.2	
Small cell lung			
Age (≤65/65–74/≥74 years)	154/150/86	39.5/38.5/22.1	66.0 (59.0–73.0)
Survival (months)			7.8 (3.5–13.6)
Weight loss in past 3 months	294	75.3	5.04 (0.8–10.2)
Weight loss category	195	50.0	
in past 3 months (%)	195	50.0	
Weight loss < 5.0%			
Weight loss > 5.1% (cancer cachexia[a])			
BMI (kg/m^2)			25.2 (22.5–28.5)
Performance status (ECOG) (0–1/2/3/4)			1 (1–2)

SD, standard deviation; IQR, interquartile range.
[a] Defined as weight loss >5%.

Table 2
The relationship between clinic-pathological factors and survival in patients with metastatic lung cancer ($n = 390$).

Parameter	n	%	Univariate		Multivariate	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Sex (M/F)	341/49	87.4/12.6	0.60 (0.41–0.88)	0.009		
Age (≤65/65–74/≥74 years)	154/150/86	39.5/38.5/22.1	1.28 (1.08–1.50)	0.004		
Tumor type (NSCLC versus SCLC)	288/102	73.8/26.2	1.39 (1.10–1.77)	0.007		
Weight loss (%) category in past 3 months (1/2)[a]	195/195	50.0/50.0	1.49 (1.18–1.88)	0.001		
Performance status (ECOG) (0–1/2/3/4)	271/75/31/13	69.5/19.2/7.9/3.3	1.90 (1.65–2.18)	<0.001	1.74 (1.50–2.02)	<0.001
mGPS (0/1/2)	103/183/104	26.4/46.9/26.7	1.84 (1.54–2.19)	<0.001	1.67 (1.40–2.00)	<0.001

[a] Weight loss (%) category: 1 = weight loss <5%, 2 = weight loss >5.1% (cancer cachexia).

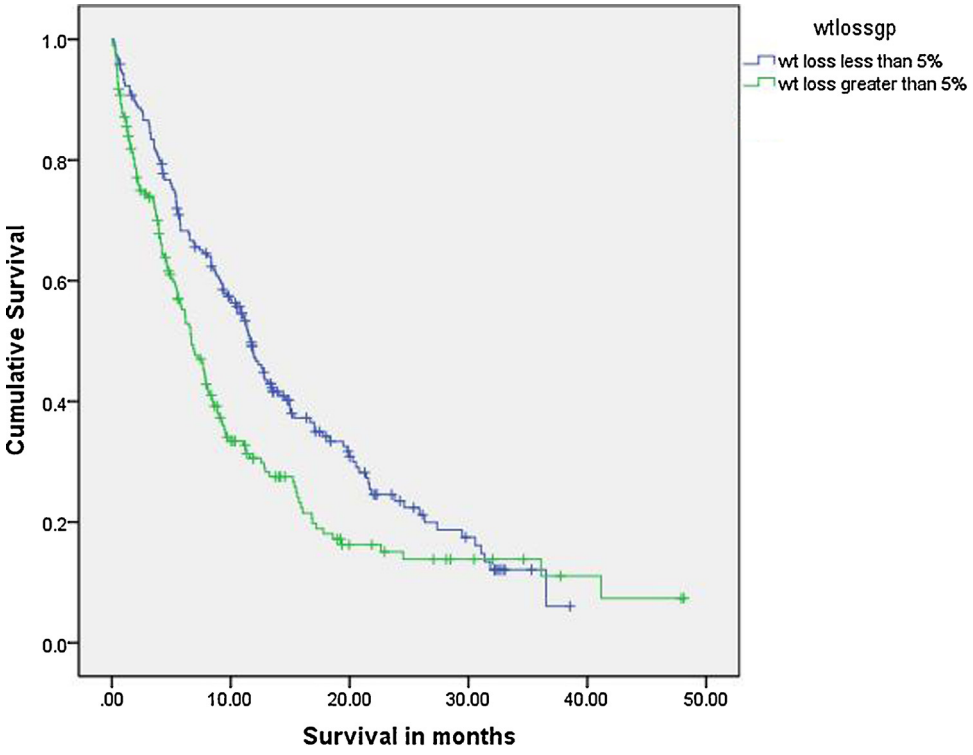

Fig. 1. Weight loss is associated with reduced survival (log rank $p = 0.001$). The area under the receiver operator curve (ROC) was 0.49 (95% CI = 0.43–0.55), $p = 0.661$.

Figs. 1–3 show Kaplan–Meier survival curves for weight loss, performance status and mGPS respectively.

Table 3 shows the relationship between survival at 3 months and mGPS and performance status. Survival was compared across all categories for both mGPS and performance status. For performance status, survival at 3 months ranged from 99% (ECOG 0–1) to 74% (ECOG 2). For mGPS, survival at 3 months ranged from 99% (mGPS0) to 71% (mGPS2). When used in combination, survival at 3 months ranged from 99% (mGPS 0 and ECOG 0–1) to 33% (mGPS = 2 and ECOG 3). Performance status does correlate with mGPS (Pearson coefficient is 0.0206, $p < 0.001$) however this must be taken in the context of the large sample size so limited inference can be drawn from this.

Table 3
The relationship between mGPS and performance status and the survival rate (%) at 3 months in patients with metastatic lung cancer ($n = 390$).

Performance status (ECOG grouping)	mGPS 0	mGPS 1	mGPS 2	mGPS 0–2
0–1	99% $n = 79$	95% $n = 133$	71% $n = 59$	91% $n = 271$
2	74% $n = 19$	71% $n = 34$	59% $n = 22$	68% $n = 75$
3	$n = 4$	55% $n = 12$	33% $n = 15$	44% $n = 31$
4	$n = 1$	$n = 4$	$n = 8$	23% $n = 13$
0–4	92% $n = 103$	87% $n = 183$	58% $n = 104$	81% $n = 390$

Where $n < 10$, analysis not performed.

4. Discussion

The results of this study show that age, sex, weight loss, tumor type, performance status and markers of the systemic inflammatory response (mGPS), all have prognostic value in patients with advanced lung cancer. Performance status and the mGPS carry the greatest prognostic value, however it is of interest that the mGPS has strong prognostic accuracy and performs almost identically to performance status. In addition, the combination of performance status and mGPS points to a new method of prognosis in advanced lung cancer.

Performance status (measured either by Karnofsky or ECOG classification) still remains the gold standard prognostic measure and the results of the present study support this [13,14]. However, the key limitation of performance status is that it is an entirely subjective assessment of a patient's physical activity and functioning [15–17]. It has been shown that marked discrepancies often

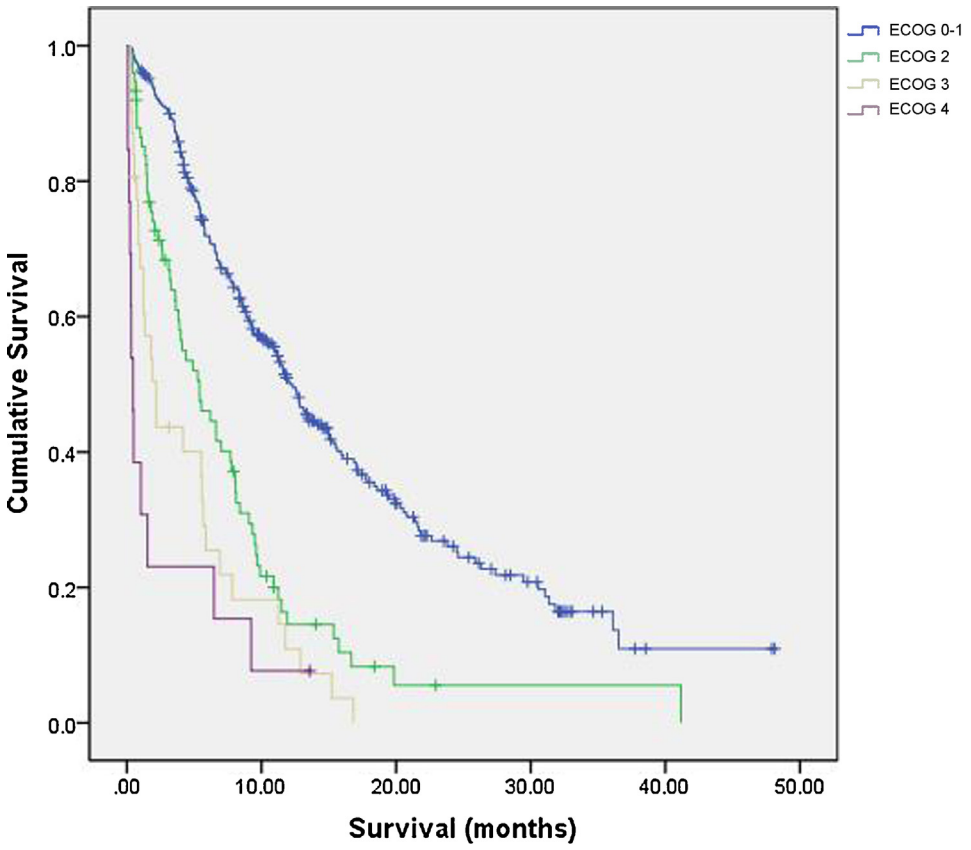

Fig. 2. Decreasing performance status was associated with reduced survival (log-rank $p < 0.001$). The area under the ROC was 0.62 (95% CI = 0.56–0.68), $p < 0.001$.

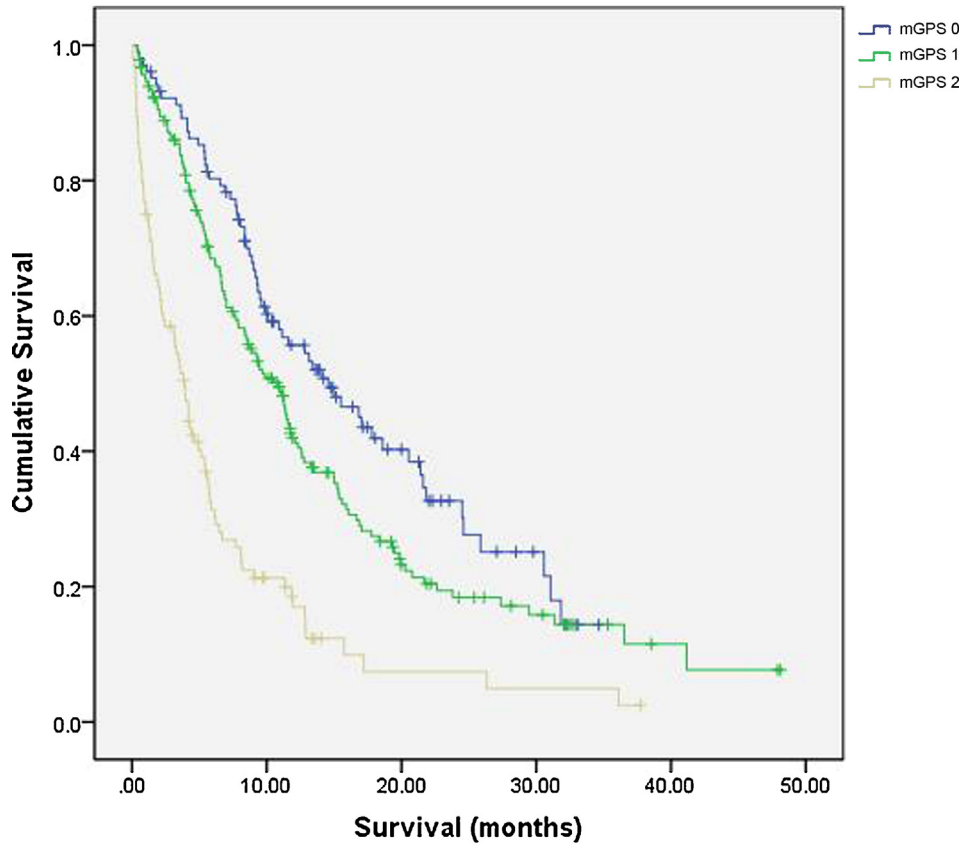

Fig. 3. Increasing mGPS was associated with reduced survival (log-rank $p < 0.001$). The area under the ROC was 0.61 (95% CI = 0.55–0.67), $p = 0.001$.

exist between clinicians' and patients' assessments of performance status [18]. Furthermore, clear inter-observer variability has been demonstrated [19]. Therefore it is important that the limitations of using a prognostic measure which is subjective and is variable, such as performance status, are considered. This aspect is of fundamental importance when the majority of treatment decisions in advanced lung cancer are deeply influenced by performance status.

In contrast, the mGPS has clear advantages. These findings support that the mGPS has independent prognostic value in advanced lung cancer, however a clear advantage over performance status is that it is objective and has 100% inter-observer congruence. It is simple to measure, inexpensive and is widely available. Used either in isolation or, perhaps even more, in combination with performance status, the present findings demonstrate its relevance in increasing accuracy of survival prediction in metastatic lung cancer [20]. This has been shown in other cancer types [21].

The findings also suggest that the role of weight loss in advanced lung cancer should be viewed with caution. Weight loss has long been regarded a "poor" prognostic sign in lung cancer. This study specifically reviewed weight loss greater than 5%. Cancer cachexia is defined as weight loss greater than 5% and felt by many to be the most adverse weight related prognostic factor in cancer. However the findings suggest that the use of weight loss as an early, prognostic factor in lung cancer is of considerably less value than performance status and mGPS and should not be assessed routinely in the clinic. For this to happen it would mean a change of mind set, as weight loss is a source of concern for patients, families and clinicians. It is regularly recorded at clinic appointments and may be used as a trigger for more investigations (suspected disease recurrence/progression) and dietetic referral or as a starting point for end of life discussions. In addition, the confirmation of weight loss in cancer is often upsetting for patients/families and they need to receive information regarding how to manage this. The findings also demonstrate that cachexia (as per current definition) [11] and BMI did not offer additional prognostic value in the presence of performance status and mGPS. However, if these factors have limited prognostic, their relative value should be re-evaluated.

There is an urgency for improved survival prediction in metastatic lung cancer. Recent work has demonstrated that approximately 10% of metastatic lung cancer patients receive anti-cancer therapy in the last 30 days of life [22], and patients with the shortest survival time after diagnosis received more anti-cancer therapy near the end of life. A key consideration in deciding appropriate treatment in an advanced lung cancer patient is prognosis. In these patients, the benefits of anti-cancer therapy must be weighed against potential disadvantages, such as multiple hospital visits, side effects and potentially life-threatening toxicity. Accurate assessment of prognosis is needed to inform such complex decisions between patients and clinicians.

The results of the present study show that the combination of mGPS and performance status are more accurate in survival prediction than either in isolation. This has been shown in other cancer types and has now been demonstrated in advanced lung cancer [21]. Using the combination of mGPS and performance status may have considerable application in considering treatment options in advanced lung cancer; for example when to use chemotherapy in patients near the end of life. This approach has been supported in recent work which has shown the value of using the mGPS as a stratification factor in very advanced disease to reduce chemotherapy use [22]. The present study takes this approach one step further by combining mGPS with performance status, to increase prognostic accuracy. This novel approach could then be used to guide the choice of oncology treatment in advanced lung cancer patients.

The present study has several limitations. There was a high proportion of men and SCLC in the cohort studied in keeping with the epidemiology of lung cancer in Greece. Furthermore not all previously studied prognostic factors in advanced NSCLC have been examined. However as performance status remains the gold standard prognostic measure in use clinically, its inclusion here is important. Details on cancer treatment, EGFR mutations and histological subtype (for NSCLC) are not available and this would be of interest to assess the effect of response of chemotherapy in patients in poor prognostic groups. All patients in the study were due to start anti-cancer therapy and therefore the number of patients with PS 3 or 4 was small.

5. Conclusion

Performance status and mGPS are superior prognostic factors in metastatic lung cancer and in combination increase survival prediction in advanced lung cancer. In translating this to clinical care, these factors should now be examined in the setting of treatment stratification in the complex area of advanced lung cancer. Continuing studies are eagerly awaited.

Conflicts of interest

There are none to declare.

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